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The Stereochemistry of Optically Active Thio-derivatives of Phosphorus-based Acids

M.Mikołajczyk and M.Leitloff

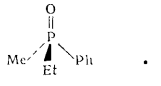
The review deals with the literature on the separation of chiral thio- and seleno-derivatives of phosphorus-based acids into optical isomers and their most important stereospecific transformations are discussed. Particular attention is concentrated on the analysis of the configurational relations between chemical and physicochemical methods for the determination of the absolute configurations of optically active thio-derivatives of phosphorus-based acids.
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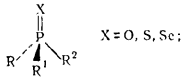
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I. INTRODUCTION

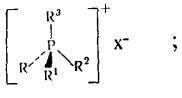
The stereochemistry of organic compounds containing a heteroatom in the molecule as the centre of asymmetry began to develop at the beginning of the present century. At the same time the first attempts were made to resolve chiral organophosphorus compounds into optical isomers. In 1911 Meisenheimer and Lichtenstadt[1] obtained the optically active ethylmethylphenylphosphine oxide and demonstrated for the first time the steric configuration of tetracoordinate phosphorus derivatives:



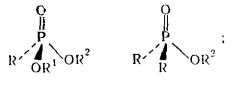
Although subsequently many investigators attempted to resolve chiral organophosphorus compounds, in the course of several decades these were successful in only a few cases. The failure of the majority of the experiments was due to the difficulties associated with the selection of the appropriate resolving agent, forming crystalline diastereoisomers with the test compounds. It was not until the 1950s that much progress was achieved in this field. Many phosphorus compounds which have been resolved into optical isomers are now known. They can be combined into at least six main classes, namely:
(a) phosphine oxides, sulphides, and selenides[2-4]:



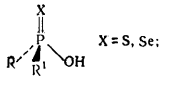
(b) quaternary phosphonium salts[5,6]:



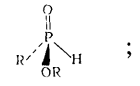
(c) esters of phosphonic and phosphinic acids[7]:



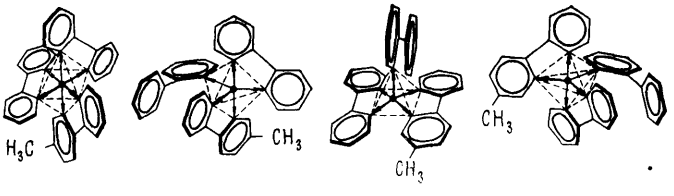
(d) thio- and seleno-derivatives of phosphorus-based acids:



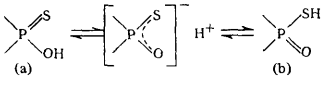
(e) phosphinates[8-20]:



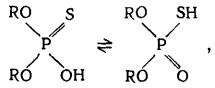
(f) compounds of pentacovalent and hexacovalent phosphorus[21]:



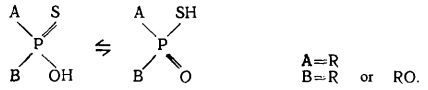
The recent considerable progress in research on the stereochemistry of phosphorus has been reflected in many reviews[6,22-29]. Together with optically active phosphine oxides and quaternary phosphonium salts, monothio-derivatives of phosphorus-based acids are of greatest importance for the development of the stereochemistry of organophosphorus compounds. The special role of these compounds in phosphorus chemistry is a consequence of their high reactivity and interesting chemical structure. In contrast to the oxygen-containing phosphorus-based acids >P(O)OH and the dithio-derivatives of phosphorus-based acids >P(S)SH, the monothio-derivatives can exist in two tautomeric forms: thionic (a) and thiolic (b):



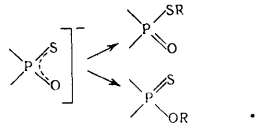
The tautomeric equilibrium between these compounds has been investigated in detail by Kabachnik et al.[30], who showed that both tautomeric forms of dialkylphosphorothioic acids are involved in the equilibrium in comparable amounts:



while in the case of phosphonothioic and phosphinothioic acids the equilibrium is almost completely displaced towards the thionic form:



The monothioacids have ambident anions[31, 32] which can react in two ways with electrophilic agents with the consequent formation of two types of derivatives: thiolo- and thiono-:



The reactivity of the anion can be satisfactorily accounted for with the aid of Pearson's concept[33,34] of "hard" and "soft" acids and bases. The "hard" basic centre of the anion is the more electronegative oxygen atom, which reacts more readily with "hard" acid centres, such as the phosphoryl or thiophosphoryl phosphorus atom, the silicon atom in silyl halides, the carbon atom in the carbonyl group, etc. On the other hand, the sulphur atom in the anion of the thioacid, which is a "soft" base, reacts more readily with "soft" electrophilic agents such as the sp^3-hybridised carbon atom in alkyl halides or halogen cations.

After the publication of the first successful experiments on the resolution of chiral thio-derivatives of phosphorus-based acids into optical isomers, the rapid development of the search for new easy methods of synthesising other representatives of compounds of this class began. At the same time research was started on the stereochemistry of the reactions of optically active thio-derivatives of phosphorus-based acids, the main aim of which was to investigate the stereochemistry of nucleophilic substitution at the asymmetric phosphoryl and thiophosphoryl centres. The studies by Aaron in the USA, Hudson in England, and Michalski and Ratajczak and Mikolajczyk in Poland have been of great importance in the development of the dynamic stereochemistry of thio-derivatives of phosphorus-based acids.

In studies on the stereochemistry of phosphorus much attention has been devoted recently to the problem of the absolute configuration of the optically active thioacids in connection with their exceptionally important position in the numerous family of chiral phosphorus compounds and the great biological activity of some of their derivatives (particularly thiolate esters and acid fluorides). Vigorous research during the last five–six years led to the determination of the absolute configurations of almost all the known optically active thioacids and to the development of many convenient chemical and physicochemical methods for the determination of the chirality of the phosphorus atom in the thioacids.

The above considerations led the present authors to write this review of research on the stereochemistry of thio-derivatives of phosphorus-based acids, which constitutes the first survey of the results of studies on the absolute configurations of the chiral acids together with a description of data concerning methods for their resolution into optical isomers and the analysis of their stereospecific transformations.

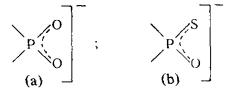
II. METHODS FOR THE SEPARATION OF CHIRAL PHOSPHORUS-BASED THIOACIDS INTO OPTICAL ISOMERS

The first attempts at the separation of phosphorus-based acids into optical isomers were undertaken as early as 70 years ago. However, initially attention was concentrated mainly on unsuccessful attempts to resolve oxygen-containing phosphorus-based acids:



The names of Caven[35], Kipping[36], Pope[37], Gibson[37], Ephraim[38], Arbuzov[39], and many other investigators are associated with research in this field.

The study by Ephraim (1911), who demonstrated that oxygen-containing phosphorus-based acids cannot be separated into optical isomers since their anions (a) are symmetrical, merits special attention:

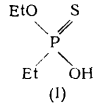


Ephraim was the first to draw attention to the fact that the substitution of one of the oxygen atoms by a sulphur atom leads to the formation of an asymmetric anion (b) and his further research was concerned with the resolution of chiral monothio-derivatives of phosphorus-based acids. However, his first attempt at the resolution of phosphoramidothioic acid,



was unsuccessful, since this acid did not form crystalline diastereoisomeric salts with the alkaloids which he had chosen. The later attempts by Arbuzov and Kamai[39] to resolve chiral thio-derivatives of phosphorus-based acids were likewise unsuccessful for the same reason.

It was not until 1956 that Aaron and Miller[40,41] succeeded for the first time in separating a chiral thioacid of phosphorus into enantiomers. This was *O*-ethyl ethylphosphonothioic acid (I), which was separated into optical isomers with the aid of the alkaloids quinine and brucine:



A somewhat simplified process for the preparation of this acid was described later by Michalski and Ratajczak[42].

In recent years Aaron and coworkers[43] resolved a series of *O*-alkyl alkylphosphonothioic acids (II–VI) by the fractional crystallisation of their diastereoisomeric salts with quinine:



(II) R=Me, R^1=Me; (V) R=Et, R^1=Me;
(III) R=Me, R^1=Et; (VI) R=i-Pr, R^1=Et.
(IV) R=Me, R^1=i-Pr;

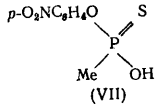
The characteristics of the optical isomers which they obtained are given in Table 1.

Table 1. Characteristics of the optical isomers of *O*-alkyl alkylphosphonothioic acids $(R^1O)R^2P(S)OH$.

№	R^1	R^2	Resolving amine	Dicyclohexylammonium salt			References
				m.p., °C	(+)$[\alpha]_D$,°	(-)$[\alpha]_D$,°	
I	C_2H_5	C_2H_5	quinine	160	6.94 (13.205)[a]	7.11 (13.6)[a]	41
II	CH_3	CH_3	a) quinine b) α-phenyl ethylamine	180	6.6 6.37	2.3 6.35	43 45
III	C_2H_5	CH_3	a) quinine b) α-phenyl ethylamine	127	7.0 (9.6)[a] 8.47	4.2 8.47	43 45
IV	i-C_3H_7	CH_3	a) quinine b) α-phenyl ethylamine	126	7.6(13.6)[a] 7.76	7.6(13.9)[a] 7.72	43 45
V	CH_3	C_2H_5	quinine	185	4.1	7.0	43
VI	C_2H_5	i-C_3H_7	quinine	149	6.5	7.0	43
VII	p-$NO_2C_6H_4$	CH_3	—	—	—	—	44
VIII	n-C_4H_9	CH_3	α-phenyl ethylamine	116	7.25	7.21	45
IX	CH_3	t-C_4H_9	α-phenyl ethylamine	—	13.18[a]	10.5[a]	46
X	CH_3	i-C_3H_7	α-phenyl ethylamine	180	4.6	4.2	47
XI	n-C_3H_7	CH_3	α-phenyl ethylamine	—	1.3[a]	1.06[a]	48

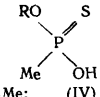
[a] Free acid.

In 1963 Boter and Ooms[44] separated *O*-p-nitrophenylmethylphosphonothioic acid (VII) into optical isomers:



(VII)

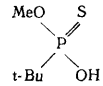
In his search for a simple method of synthesising optically active Sarin, one of the most important inhibitors of cholinesterase, Boter[45] developed in 1967 a new method for the separation of chiral *O*-alkyl methylphosphonothioic acids (II–IV, VIII):



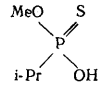
(II) R=Me; (IV) R=i-Pr;
(III) R=Et; (VIII) R=n-Bu.

He used optically active α-phenylethylamine (both optical isomers) as the resolving agent. The first stage in the resolution consisted in the introduction of half a mole of the dextrorotatory amine into an etheral solution of one mole of the racemic acid and the separation of the rapidly crystallised salt of the (+)-amine with the (+)-thioacid. In the second stage the acid remaining in solution was treated with an equimolar amount of the laevorotatory amine and the diastereoisomeric salt of the latter with the laevorotatory acid was isolated.

α-Phenylethylamine is nowadays finding extensive application in the separation of chiral thio-derivatives of phosphorus acids in view of its ability to form readily crystallisable salts and because of the ready availability of both its enantiomers. The resolution by this amine of *O*-methyl t-butylphosphonothioic acid (IX) by Krawiecka and Michalski[46] and of *O*-methyl isopropylphosphonothioic acid (X) by Mikołajczyk and Omelańczuk[47] can serve as examples:



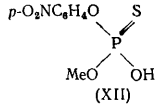
(IX)



(X)

Leitloff[48] attempted to separate *O*-propyl methylphosphonothioic acid (XI) into optical isomers with the aid of α-phenylethylamine by Boter's method. However, the inadequate optical purity of the enantiomers obtained by this method shows that the latter must be modified for this acid.

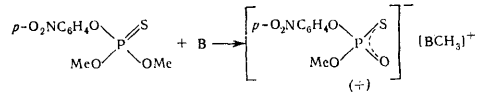
One year after the publication of Aaron's first communication concerning the separation of the optical isomers of *O*-ethyl ethylphosphonothioic acid (I) Hilgetag and Lehman[49] described a method for the separation of *O*-methyl *O*-*p*-nitrophenyl phosphorothioic acid (XII):



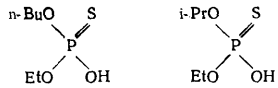
(XII)

OO-Dimethyl *O*-*p*-nitrophenyl phosphorothionate was converted by this method into the silver salt of the acid (XII) as a result of dealkylation with silver nitrate; the salt was then treated with methylstrychnine iodide. The diastereoisomeric methylstrychnine salts with the rotations $[\alpha]_D = -12.4°$ and $[\alpha]_D = +9.7°$ were separated by fractional crystallisation. In an acid medium both salts give rise to unstable optically active isomers of the acid (XII), which were converted into lead salts with the rotations $[\alpha]_D = -17.4°$ and $[\alpha]_D = +18.9°$ respectively. The optical isomers of the acid (XII) were the first examples of optically active phosphorus-based thioacids.

The same workers[50] also developed a new interesting method for the separation of the isomers of the acid (XII), which is in the nature of partial asymmetric synthesis. It consists in the asymmetric demethylation of *OO*-dimethyl *O*-*p*-nitrophenyl phosphorothionate by strychnine. The dextrorotatory salt of the thioacid with $[\alpha]_D = +13.8°$ (60–80%) predominated in the mixture of the diastereoisomeric methylstrychnine salts of the acid (XII):



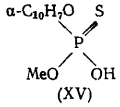
The next examples of optically active phosphorothioic acids are *O*-butyl *O*-ethyl phosphorothioic acid (XIII) and *O*-ethyl *O*-isopropyl phosphorothioic acid (XIV), which were separated into their isomers by Michalski et al.[51]



(XIII) (XIV)

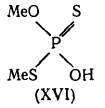
These thioacids were resolved with the aid of cinchonidine and quinine. Although the optical rotations of the resulting enantiomers of both thioacids were too low to be measured (on apparatus with a sodium source), nevertheless their derivatives were optically active, which demonstrated their partial separation.

In 1968 yet another chiral phosphoromonothioic acid was resolved, namely *O*-methyl *O*-α-naphthyl phosphorothioic acid (XV). Donninger and Hutson[52] achieved this by the fractional crystallisation of the diastereoisomeric salts of (XV) with the aid of (+)- and (−)-ephedrine:



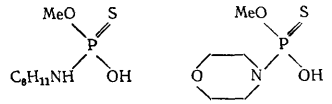
(XV)

In the following year Teichmann[53] resolved the dimethyl ester of phosphorothiolothionic acid (XVI), which contains two sulphur atoms in the molecule. The resolution was achieved by the asymmetric demethylation of *OOS*-trimethyl phosphorothiolothionate with strychnine:



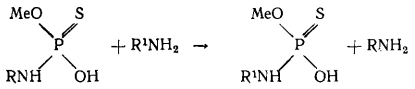
(XVI)

The optically active phosphoromidothioic acids obtained by Hamer[54] constitute a separate group. In 1965 Hamer resolved *N*-cyclohexyl *O*-methyl phosphoramidothioic acid (XVII) by the fractional crystallisation of its diastereoisomeric quinine salts:



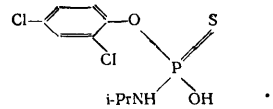
(XVII) (XVIII)

Then, by substituting the amino-residue, he obtained a whole series of optically active phosphoramidothioic acids:



Several years later Gerrard and Hamer[55] resolved by the same method *O*-methyl phosphoromorpholidothioic acid (XVIII) and isolated its dextrorotatory isomer in the form of the ammonium salt.

The methylammonium salts of both optically active forms of *O*-2,4-dichlorophenyl *N*-isopropyl phosphoramidothioic acid (XIX) were obtained in 1969 by Seiber and Tolkmith[56]. The methylammonium salt of the racemic acid (XIX), synthesised by the demethylation of the corresponding *O*-methyl phosphoramidothioate, was converted into a mixture of diastereoisomeric salts with quinine using quinine sulphate. The diastereoisomers were separated by fractional crystallisation and then, as a result of the substitution of quinine by methylamine, the enantiomeric (+)- and (−)-salts were obtained from them with the rotations $[\alpha]_D = +15.9°$ and $-23.4°$ respectively:



(XIX)

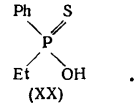
Certain physicochemical properties of optically active phosphorothioic, phosphonothioic, and phosphoramidothioic acids are listed in Table 2.

Table 2. Optically active phosphorothioic, phosphonothioic, and phosphoramidothioic acids $(R^1)R^2P(S)OH$.

№	R^1	R^2	Resolving amine	(+)$[\alpha]_D$,°	(−)$[\alpha]_D$,°	References
XII	*p*-$O_2NC_6H_4O$	CH_3	strychnine	18.9[a] 13.8[d]	17.4[a] 13.1[d]	49 50
XIII	n-C_4H_9O	C_2H_5O	cinchonidine	1.0[b]	1.3[b]	51
XIV	i-C_3H_7O	C_2H_5O	quinine	2.1[b]	2.0[b]	51
XV	α-$C_{10}H_7O$	CH_3O	ephedrine	33.0[e] 53.4[b]	45.9[e] 51.0[b]	52
XVI	CH_3S	CH_3O	strychnine	27.1[c] 14.1[d]	27.9[c] 14.5[d]	53
XVII	CH_3O	$C_6H_{11}NH$	quinine	38.0[c]	37.0[c]	54
XVIII	CH_3O	C_4H_8NO	quinine	2.9[f]	—	55
XIX	2,4-$Cl_2C_6H_3O$	*i*-PrNH	quinine	15.9[f]	23.4[f]	56

[a] Lead salt; [b] *S*-methyl ester; [c] free acid; [d] methylstrychnine salts; [e] ephedrine salt; [f] ammonium salt.

The first example of the series of phosphinothioic acids resolved into optical isomers was ethylphenylphosphinothioic acid (XX). Its partial resolution was achieved by Green and Hudson[57] in 1963 with the aid of quinine as the optically active resolving agent:



(XX)

Several years later other chiral phosphinothioic acids were resolved: methylphenylphosphinothioic acid (XXI), resolved in 1968 by Benschop's group[58], and t-butylphenylphosphinothioic (XXII), resolved in 1971 by Trippet and coworkers[59]. In both cases quinine was used as the resolving agent:



(XXI) (XXII)

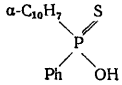
The results of studies on ethylmethylphosphinothioic acid (XXIII), partially resolved by Ratajczak, were published in the proceedings of the International Colloquium on Organic Chemistry held in Paris in 1969:[60]



(XXIII)

However, no information about the method used to resolve this acid was published.

Recently Chauzov and Lutsenko[61] resolved α-naphthylphenylphosphinothioic acid (XXIV) by the fractional crystallisation of its diastereoisomeric salts with quinine:



(XXIV)

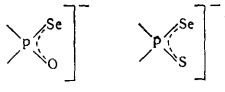
The characteristics of the optical isomers of this acid and other phosphinothioic acids are given in Table 3.

Table 3. Optically active phosphinothioic acids $R^1R^2P(S)OH$.

№	R^1	R^2	Resolving amine	(+) $[\alpha]_D$, °	(−) $[\alpha]_D$, °	References
XX	C_2H_5	C_6H_5	quinine	6.5[a]	6.5[a]	57
XXI	CH_3	C_6H_5	quinine	9.25[a]	9.22[a]	58
XXII	t-C_4H_9	C_6H_5	quinine	21.4[b]	21.4[b]	59
XXIII	CH_3	C_2H_5	—	—	—	60
XXIV	α-$C_{10}H_7$	C_6H_5	quinine	63.8[a] 112.0[b]	64.6[a] 113.0[b]	61

[a] Dicyclohexylammonium salt; [b] free acid.

An interesting class of chiral organophosphorus compounds consists of selenium-containing phosphorus-based acids and thioacids. The negative charge in the anions of these compounds is distributed between selenium and oxygen and selenium and sulphur atoms respectively:



The first example of optically active selenium-containing phosphorus-based acids was *O*-ethyl ethylphosphonothioselenoic acid (XXV), resolved into optical isomers by Krawiecki et al.[62]:



(XXV)

Recently Krawiecka et al.[63] resolved t-butylphenylphosphinoselenoic acid (XXVI) with the aid of α-phenylethylamine:



(XXVI)

Somewhat later Nuretdinov et al.[64] succeeded in resolving *O*-ethyl ethylphosphonoselenoic acid (XXVII) into optical isomers:



(XXVII)

The alkaloids quinine and brucine were used as the resolving bases. The optical rotations of the selenium-containing acids are listed in Table 4.

Table 4. Optical isomers of phosphoroselenoic acids.

No.	Resolving amine	(+) $[\alpha]_D$, °	(−) $[\alpha]_D$, °	References
XXV	quinine	4.9[a] 2.4[b]	6.7[a] 3.8[b]	62
XXIV	α-phenylethylamine	25.6[a]	30.0[a]	63
XXVII	quinine and brucine	11.36[a]	17.54[a]	64

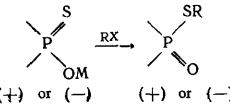
[a] Free acid; [b] dicyclohexylammonium salt.

III. STEREOSPECIFIC REACTIONS OF OPTICALLY ACTIVE PHOSPHORUS-BASED MONOTHIOACIDS

Since optically active monothio-derivatives of phosphorus-based acids have ambident anions, they are very convenient starting materials for the synthesis of thiolo- and thiono-derivatives. Further stereospecific transformations of the compounds obtained directly from the thioacids lead to the synthesis of almost all types of optically active organophosphorus compounds. A detailed description of the many-stage reactions of the thioacids would require the examination of the overall dynamic stereochemistry of phosphorus and would be outside the scope of the present review. We shall therefore consider only those reactions in which the phosphorus-based thioacids are directly involved. The study of the stereochemistry of these reactions greatly assisted in the investigation of the mechanism of nucleophilic substitution at both phosphoryl [P(O)] and thiophosphoryl [P(S)] centres[65].

Optically Active Thiolate Esters

An example of reactions in which the chiral centre is unaffected is provided by the alkylation of the salts of optically active phosphorus-based thioacids, which leads to the formation of optically active thiolate esters:



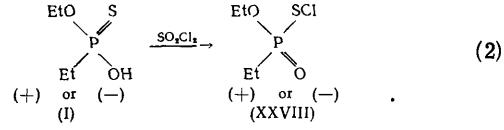
(+) or (−) (+) or (−) (1)

Alkyl halides, and among these alkyl iodides, are usually employed as alkylating agents[66-68]. Dimethyl sulphate is frequently used in the synthesis of methyl thiolate esters[57]. Since none of the bonds involving phosphorus is ruptured in the course of alkylation, the optically active thiolate esters retain the configuration of the initial thioacid.

According to Brewster's asymmetry rule, the sign of the optical rotation of the thiolate esters must be the same as that of the initial thioacids. This has been confirmed in each case described hitherto.

Optically Active Oxophosphoranesulphenyl Chlorides and Diphosphoryl Disulphides

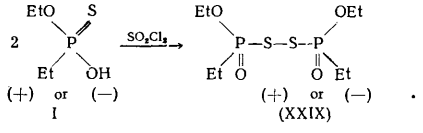
The reactions of phosphorus-based thioacids with chlorine or sulphuryl chloride leads to the formation of optically active oxophosphoranesulphenyl chlorides[42,68]. This was first discovered by Michalski and Ratajczak, who obtained optically active ethoxyethyloxophosphoranesulphenyl chloride (XXVIII) as a result of the chlorination of optically active *C*-ethyl ethylphosphonothioic acid (I):



(2)

As in alkylation, in reaction (2) the bonds involving the chiral phosphorus atom are not ruptured and the configuration of the initial thioacid is retained in the product. Optically active oxophosphoranesulphenyl chlorides are effective starting materials for further syntheses[69].

Optically active diphosphoryl disulphides can also be obtained by the reactions of optically active phosphorus-based monothioacids with sulphuryl chloride[70]. They are formed in the interaction of one molecule of sulphuryl chloride with two molecules of the thioacid:

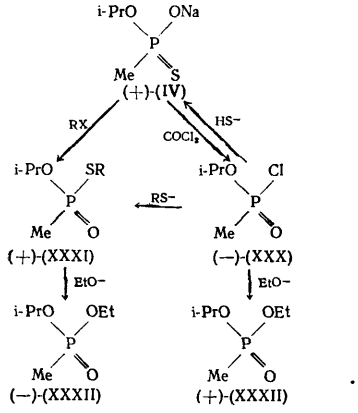


(3)

The disulphide (XXIX) is formed in two stages. Oxophosphoranesulphenyl chloride (XXVIII) is formed in the first stage and in the next stage it reacts with a second molecule of the thioacid. The chiral phosphorus atom is not attacked in either stage and the configuration of the initial acid is retained at both centres of chirality in the disulphide.

Optically Active Phosphoryl and Thiophosphoryl Halides

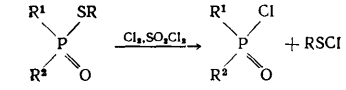
Optically active phosphorus-based monothioacids are the main starting materials for the synthesis of optically active phosphoryl [>P(O)X] and thiophosphoryl [>P(S)X] halides. One of the methods for the preparation of optically active phosphoryl chlorides involves the chlorination of salts of phosphorus-based thioacids with phosgene[66]. Aaron and Miller investigated the stereochemistry of this reaction in connection with the transformation of [−)-*O*-isopropyl methylphosphonochloridate (XXX), obtained by treating (+)-*O*-isopropyl methylphosphonothioic acid (IV) with phosgene:



(4)

The authors concluded that the reaction of the thioacid (IV) with phosgene and the formation of the compound (XXXI) take place with inversion of the configuration at the phosphorus atom.

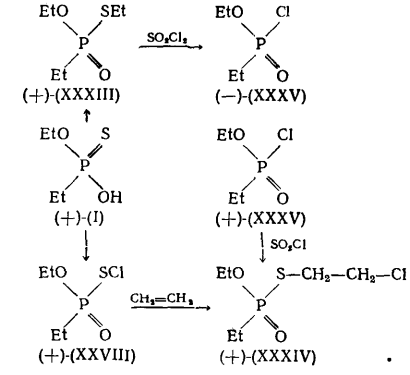
Green and Hudson[71] and independently Michalski and Ratajczak[72] obtained optically active phosphoryl chlorides by chlorinating *S*-alkyl esters of optically active phosphorus-based monothioacids:



(5)

The studies by Green and Hudson showed that chlorination of *S*-alkyl phosphinothioates leads to the formation of the corresponding chlorides with inversion of the configuration at the phosphorus atom.

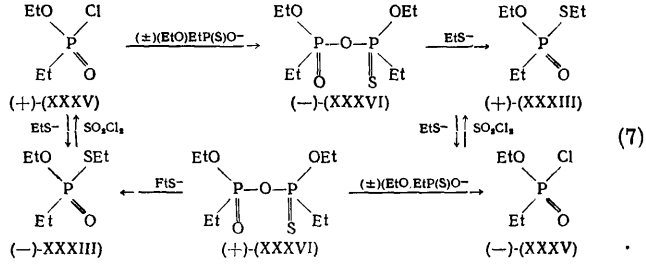
The studies of Michalski and Ratajczak led them to the conclusion that the stereochemistry of the chlorination of phosphonothioates depends on the structure of the substituent R. The mechanism of this reaction has not been elucidated so far. The studies which have been carried out hitherto suggest that the chlorination of the *S*-β-chloroethyl ester proceeds largely with retention of the configuration at the phosphorus atom, while the *S*-ethyl ester is chlorinated with inversion of configuration:



(6)

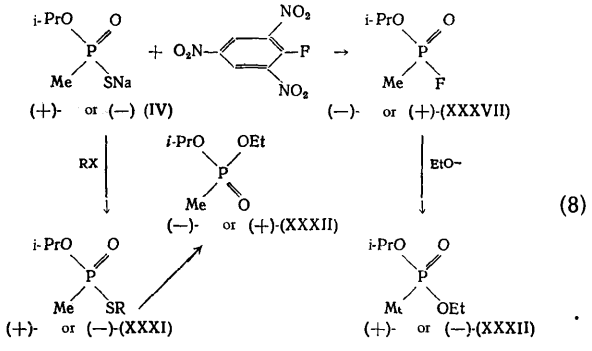
In connection with the stereochemistry of optically active phosphoryl chlorides and thiolate esters, mention should be made of the cyclic process, developed by Ratajczak[73], consisting of six reactions each of which

probably proceeds with inversion of the configuration at the phosphorus atom:



(7)

The reaction of optically active phosphorus-based thioacids with picryl fluoride leads to the formation of optically active phosphoryl fluorides. This reaction was carried out by Boter et al.[74] in the synthesis of optically active Sarin (XXXVII), the well known chlolinesterase inhibitor:



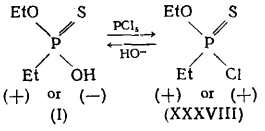
(8)

The sign of the optical rotation of the acid fluoride (XXXVII) obtained in this way is the opposite of that of the initial thioacid. Ethanolysis of the product, which is known to proceed with inversion of the configuration, leads to the formation of the ester (XXXII), which, according to Aaron, has the configuration of the initial acid. On this basis, the authors concluded that the reaction of the thioacid with picryl fluoride takes place with inversion of the configuration at the phosphorus atom.

Although phosphoryl compounds are very interesting, they are not, however, convenient objects for stereochemical studies because of their low optical stabilities†. For this reason, the results obtained can indicate only that the mechanism involving the inversion or retention of the configuration at the phosphorus atom predominates. It was found that the less reactive thiophosphoryl compounds are much more suitable for stereochemical studies.

The difference between the reactivities of phosphoryl and thiophosphoryl compounds is a consequence of the difference between the electron densities at the phosphorus atom in these compounds and the different polarisabilities of the phosphoryl and thiophosphoryl groups[75].

The synthesis by Michalski and Mikołajczak[76-78] of optically active *O*-ethyl ethylphosphonochloridothioate (XXXVIII) was an important achievement in the stereochemistry of thiophosphoryl compounds. This acid chloride is formed in a high yield and with a high optical purity in the reaction of optically active *O*-ethyl ethylphosphonothioic acid (I) with phosphorus pentachloride:

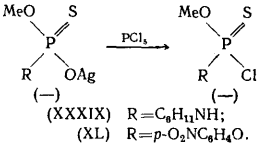


(9)

To determine the mechanism of the chlorination with phosphorus pentachloride, the resulting acid chloride (XXXVIII) was hydrolysed[78], the hydrolysis having been shown previously to involve usually the inversion of the configuration. As a result of the hydrolysis, the authors obtained the initial acid (I). This led them to the conclusion that the chlorination also proceeds with a change of configuration at the phosphorus atom. The high purity and optical activity of the resulting acid chloride (XXXVIII) make the compound a suitable starting material for the synthesis of other optically active organophosphorus compounds and for the investigation of reaction mechanisms[80].

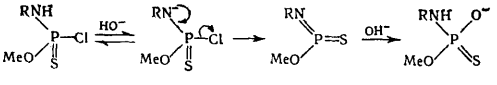
Phosphonochloridothioate derivatives of all optically active *O*-alkyl alkylphosphonothioic acids known at present were obtained similarly[81].

Using the reaction with phosphorus pentachloride, Gerrard and Hamer[82,83] also obtained optically active *O*-methyl *N*-cyclohexyl phosphoramidochloridothionate (XXXIX) and *O*-methyl *p*-nitrophenyl phosphorochloridothionate (XL):



(10)

It is interesting that alkaline hydrolysis of the phosphoramidochloridothionate (XXXIX) leads, in conflict with the above, to the formation of a racemic product, while its solvolysis results in the formation of an optically active product with inversion of the configuration. Under alkaline conditions, the hydrolysis probably proceeds via the following mechanism:



(11)

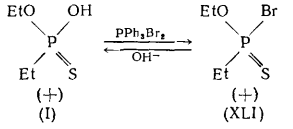
and the racemisation is associated with the formation of an intermediate optically inactive analogue of metaphosphate.

In contrast to the silver salts of optically active phosphorus-based thioacids, their ammonium salts are not convenient starting materials for the synthesis of optically active pure phosphorochloridothionates. Seiber and Tolkmith[56] showed that the reaction of the optically active methylammonium salt of *O*-2,4-dichlorophenyl *N*-isopropyl phosphoramidothioic acid (XIX) with phosphorus pentachloride results in the formation of a partly racemised product (probably via a chlorine–chlorine exchange reaction at the phosphorus atom).

Michalski et al.[84] found that optically active thiophosphonyl bromides can be obtained as a result of the reaction of triphenylphosphine dibromide with optically active

† Optically active phosphoryl halides with high optical stability were obtained recently from phosphorus-based thioacids in which the phosphorus atom is linked to a t-butyl group[63].

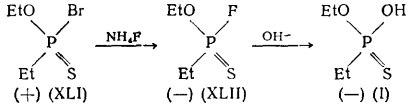
phosphorus-based monothioacids. Optically active *O*-ethyl ethylphosphonobromidothionate (XLI) was obtained by this method:



(12)

Hydrolysis of compound (XLI) leads to the reformation of the initial acid. This proves that the bromination of the thioacid with triphenylphosphine dibromide takes place with inversion of configuration at the phosphorus atom.

It is noteworthy that the optically active phosphonofluoridothionate (XLII) can be obtained from the optically active phosphonobromidothionate (XLI) as a result of the substitution of the bromine atom by a fluorine atom using ammonium fluoride[85]:

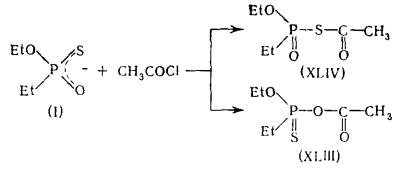


(13)

The result of the hydrolysis of compound (XLII) shows that the halogen exchange reaction is accompanied by the inversion of configuration.

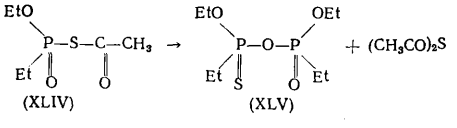
Optically Active *O*-Acyl Phosphonothionates

Omelańczuk and coworkers[86,88] studied compounds of this type and found that *O*-acetyl and *S*-acetyl anhydrides are formed in the reaction of a salt of the optically active *O*-ethyl ethylphosphonothioic acid (I) with acetyl chloride:



(14)

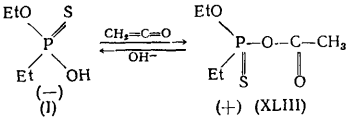
In contrast to the *O*-acetyl anhydride (XLIII), which can be readily isolated, its thiolo-isomer (XLIV) is unstable and "disproportionates" under the reaction conditions with formation of optically active *OO*-diethyl diethylpyrophosphonothioate (XLV) and diacetyl sulphide:



(15)

The ability of the thioacid anion to react in two different ways with acetyl chloride and to form similar decomposition products of the thiol type was observed by Kabachnik and coworkers[87] in the acetylation of diethylphosphinothioate salts.

Mikołajczyk et al.[88] modified the acetylation procedure using the free thioacid instead of its salt and developed a new method for the synthesis of active acetylthiophosphoryl anhydrides in the reaction of optically active phosphorus-based thioacids with keten. They showed that in the acetylation of the free acid with both acetyl chloride and acetic anhydride the amount of disproportionation products of the thiol anhydride (XLIV) diminishes appreciably and the yield of the *O*-acetylanhydride (XLIII) increases. On the other hand, the reaction with keten leads to the exclusive formation of the *O*-acetylation product:

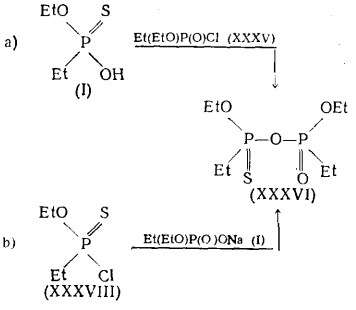


(16)

The configuration of the resulting anhydride (XLIII) corresponds to that of the initial acid, since the centre of chirality is not involved in the reaction. This was confirmed by the hydrolysis of the (+)-isomer of (XLIII) which yielded the initial (−)-acid (I). As expected, in this case the attack by the hydroxy-group is directed to the most electrophilic centre in the molecule, i.e. to the carbonyl group. The configuration of the thioacid residue, which is the group eliminated, does not change.

Optically Active Pyrophosphonothioates and Pyrophosphonodithioates

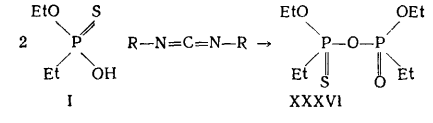
Pyrophosphonomonothioates and pyrophosphonodithioates have been the subject of research by Michalski for several years[89]. The optically active *OO*-diethyl diethylpyrophosphonothionate (XLV) [90] is particularly convenient to investigate because of its ready availability. The starting material for the synthesis is *OO*-ethyl ethylphosphonothioic acid (I) or *O*-ethyl ethylphosphonochloridothioate (XXXVIII) [91] obtained from it:



(17)

Pyrophosphonothioates with one or two optically active centres can be obtained via pathway (a) indicated above. However, in view of the low stability of *O*-ethyl ethylphosphonochloridate (XXXV), the pyrophosphonothioate with two optically active phosphorus atoms obtained in this way has a low optical purity of the phosphoryl centre.

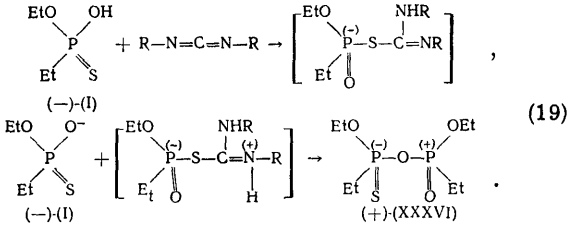
Mikołajczyk[92] developed an interesting method for the synthesis of pyrophosphonothioates with two optically active centres by the reaction of an optically active thioacid with dicyclohexylcarbodiimide:



(18)

OO-Diethyl diethylpyrophosphonothioate (XXXVI) obtained by this method has a high optical purity of the phosphoryl centre. This reaction proceeds in two stages and leads

to the formation of the optically active pyrophosphonothioate (XXXVI) with the opposite configurations at the phosphorus atoms:



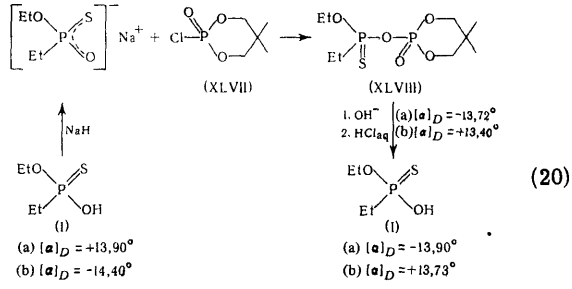
(19)

The relative configurations and the optical purities of both chiral centres in pyrophosphonothioates of this type can be readily determined by cleaving them with nucleophilic agents. The cleavage of compound (XXXVI) is associated exclusively with attack on the phosphoryl centre P(O) and takes place with inversion of the configuration at the attacked phosphorus atom. The thioacid residue is the group eliminated and its configuration is unaltered in the cleavage reaction.

Stereochemical studies on the cleavage of other pyrophosphonothioates showed that nucleophilic attack can be directed also to the thiophosphoryl centre, depending on the type of substituent at the two phosphorus atoms and on the reaction medium.

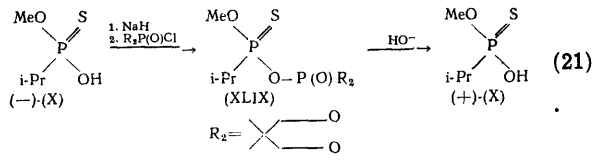
The Walden cycle, developed by Michalski et al.[93], in which the authors employed pyrophosphonothioates (XLVIII) with marked steric hindrance at the phosphoryl centre, merits particular attention in connection with this research.

As a result of two consecutive reactions, condensation of the thioacid (I) with 2-chloro-5,5-dimethyl-2-oxo-1,3-dioxa-2-phosphorinane (XLVII) followed by hydrolysis, one of the enantiomers of *O*-ethyl ethylphosphonothioic acid was converted into its antipode. Since the condensation reaction does not affect the symmetry of the chiral centre, this result proves unambiguously that alkaline hydrolysis proceeds with inversion of configuration at the thiophosphoryl phosphorus atom:



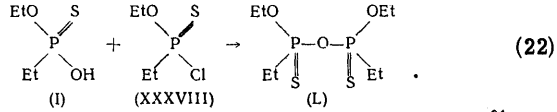
(20)

The Walden cycle was developed for *O*-methyl isopropylphosphonothioic acid (X) in order to demonstrate that nucleophilic substitution in isopropylphosphonothioates proceeds in the same way as in ethylphosphonothioates, i.e. with inversion of the configuration at the phosphorus atom[81]:



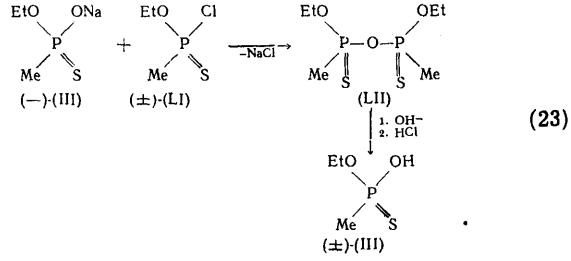
(21)

Pyrophosphonodithioates are formed as a result of the reaction between an optically active thioacid and a phosphonochloridothioate[91,94]:



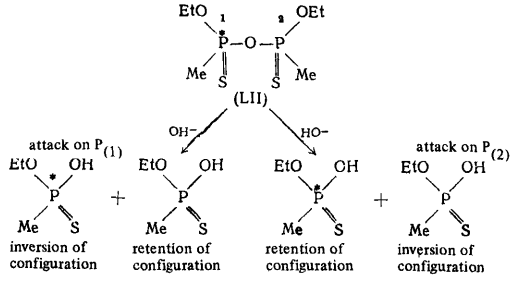
(22)

Using pyrophosphonodithioates, Green and Hudson[94] investigated for the first time nucleophilic substitution at the thiophosphoryl centre and found that it proceeds with inversion of the configuration at the phosphorus atom. They studied the hydrolysis of the optically active *OO*-diethyl dimethylpyrophosphonodithioate (LII), obtained by the reaction of a salt of the optically active acid (III) with (+)-*O*-ethyl methylphosphonochloridothionate (LI):



(23)

They found that the hydrolysis leads to the formation of racemic *O*-ethyl methylphosphonothioic acid (III). There are two equivalent phosphorus atoms in pyrophosphonodithioates. Consequently attack by the nucleophilic agent can be directed with equal probabilities to both thiophosphoryl centres. The formation of the racemic acid (III) as a result of the hydrolysis of the pyrophosphonodithioate (LII) with one optically active centre demonstrates the inversion of the configuration at the phosphorus atom. The interpretation of the results obtained by Green and Hudson may be illustrated by the following scheme:



(24)

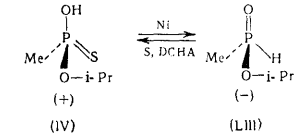
Further studies on the alcoholysis, mercaptanolysis, and aminolysis of *OO*-diethyl diethylpyrophosphonodithioates[86,88] confirmed that nucleophilic substitution at the thiophosphoryl centre proceeds with inversion of the configuration.

Optically Active Phosphonites

Much attention has been devoted recently to optically active phosphonites:



Reiff and Aaron[12] found that desulphuration of optically active phosphonothioic acids in the presence of nickel as the catalyst is a convenient method for the synthesis of compounds of this type. On heating (*R*)-(+)-*O*-isopropyl methylphosphonothioic acid (IV) in ethanol in the presence of Raney nickel, they obtained the optically active (*S*)-(−)-*O*-isopropyl methylphosphonite (LIII):



(25)

(+) (IV) (−) (LIII)

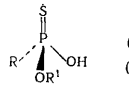
DCHA = dicyclohexylamine.

The addition of sulphur to the resulting phosphonite in the presence of dicyclohexylamine, which undoubtedly takes place with the retention of the configuration, leads to the reformation of the initial acid. This shows that desulphuration of the acid proceeds without a change in the configuration at the phosphorus atom.

Another method for the synthesis of optically active phosphonites involves their stereospecific inclusion in cyclodextrins[14,18].

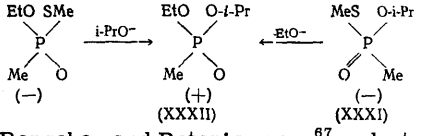
IV. DETERMINATION OF THE CONFIGURATIONS OF OPTICALLY ACTIVE PHOSPHORUS-BASED MONOTHIOACIDS BY CHEMICAL CORRELATION‡ AND X-RAY DIFFRACTION

The relative configurations of optically active monothioacids were mentioned for the first time by Aaron et al.[43], who described the resolution of chiral *O*-alkyl alkylphosphonothioic acids (I–VI) into optical isomers. Studies on the biological activities of the corresponding derivatives synthesised from the optically active thioacids showed that the optical isomers obtained from the (−)-thioacids are much more powerful inhibitors of cholinesterases than the enantiomers obtained from the (+)-thioacids. On this basis the authors concluded that the *O*-alkyl alkylphosphonothioic acids (I–VI) with the same sign of optical rotation have the same configuration:



(I) R = Et, R¹ = Et; (IV) R = Me, R¹ = i-Pr;
(II) R = Me, R¹ = Me; (V) R = Et, R¹ = Me;
(III) R = Me, R¹ = Et; (VI) R = i-Pr; R¹ = Et

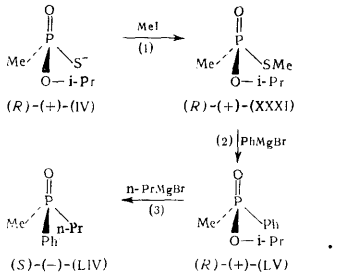
This conclusion was confirmed also by the chemical correlation of the (−)-isomers of *O*-isopropyl methylphosphonothioic (IV) and *O*-ethyl methylphosphonothioic (III) acids:



(26)

(−) (XXXII) (+) (XXXI) (−)

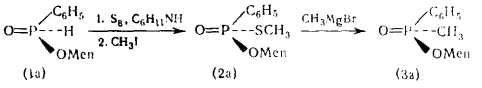
In 1968 Benschop and Boter's group[67] undertook studies whose aim was to determine the absolute configurations of the anticholinesterases obtained from optically active *O*-isopropyl methylphosphonothioic acid (IV); it was therefore necessary to elucidate the absolute configuration of the initial thioacid (IV). Benschop and Boter chose the method of chemical correlation between (+)-*O*-isopropylmethylphosphonothioic acid and (*S*)-(−)-methylphenyl-n-propylphosphine oxide (LIV). Their chemical comparison of the configurations is illustrated below:



(27)

(*R*)-(+)-(IV) (*R*)-(+)-(XXXI) (*S*)-(−)-(LIV) (*R*)-(+)-(LV)

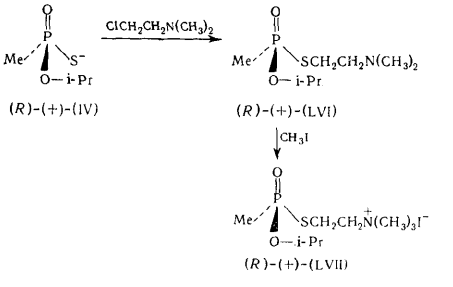
The thioacid (IV) was converted into the phosphine oxide (LIV) by three stereospecific reactions. The first of these (*S*-methylation) proceeds with retention of the configuration at the phosphorus atom[66]. As shown previously[95,96], the third reaction is accompanied by the inversion of the configuration. Consequently the correct determination of the configuration of the (+)-thioacid (IV) requires the knowledge of the stereochemistry of reaction (2):



(1a) (2a) (3a)

Benschop and Boter initially postulated that this reaction proceeds with inversion of the configuration at the phosphorus atom (as in the analogous nucleophilic substitution reactions at the phosphorus atom in similar systems). However, the latest reports[97], which have been confirmed by X-ray diffraction data, indicate that the stereospecific conversion of phosphonothiolates into the corresponding phosphinates proceeds with retention of the configuration at the phosphorus atom§.

Knowing the absolute configuration of the phosphine oxide and the stereochemistry of the successive chemical transformations, the configuration of *O*-isopropyl methylphosphonothioic acid (IV) was determined as (*R*)-(+). The final proof of the correctness of the determination of the absolute configuration of *O*-isopropyl methylphosphonothioic acid was obtained by X-ray diffraction[98] of the *S*-alkyl ester (LVII) synthesised from the (+)-acid (IV) as a result of reactions which do not affect the symmetry of the chiral centre:



(28)

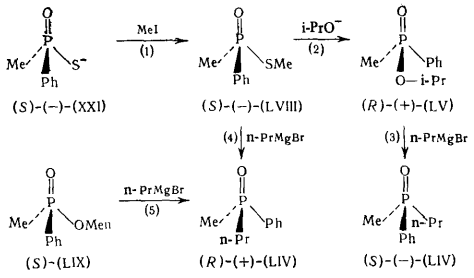
(*R*)-(+)-(IV) (*R*)-(+)-(LVI) (*R*)-(+)-(LVII)

‡ The chemical correlation method involves the determination of the configurations of optically active compounds by chemical reactions which relate compounds of known configuration to those whose configuration is to be determined.

§ The retention of the configuration when phosphonothiolates are acted upon by Grignard reagents has been demonstrated by X-ray diffraction of the phosphonothiolate (2a), which is an intermediate in the conversion of (*R*p)-*O*-menthyl phenylphosphonite (1a) into (*R*p)-*O*-menthyl methylphenylphosphinate (3a).

The absolute configuration of the ester (LVII) was determined by X-ray diffraction as (*R*)-(+), since the initial *O*-isopropylmethylphosphonothioic acid (IV) should also have the (*R*)-(+)-configuration.

Using the same procedure, involving extrapolation to phosphine oxide, Benschop and Boter determined the absolute configuration of methylphenylphosphinothioic acid (XXI):

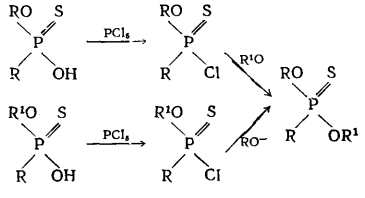


(29)

The acid (XXI) and the phosphinothiolate (LVIII) obtained from it have the same absolute configurations, since *S*-methylation does not affect any of the bonds involving the phosphorus atom. The reaction involving the synthesis of methylphenyl-n-propylphosphine oxide (*R*)-(+)-(LIV) from (*S*p)-menthyl methylphenylphosphinate (LIX) in the presence of n-propylmagnesium bromide [reaction 5, scheme (29)] proceeds with inversion of the configuration. Therefore Benschop and Boter suggested that the similar reaction of isopropyl methylphenylphosphinate (LV) with n-propylmagnesium bromide (reaction 3) also takes place with inversion of the configuration at the phosphorus atom. It is known that the substitution of the methylthio-group by an alkoxy-group (reaction 2) leads to a change in the configuration of the phosphoryl centre. Thus the conversion of (*S*)-(−)-phosphinothiolate (LVIII) into (*S*)-(−)-phosphine oxide (LIV), occurring as a result of two consecutive reactions proceeding with inversion of the configuration, enabled the authors to attribute the absolute (*S*)-configuration to (−)-methylphenylphosphinothioic acid (XXI).

On the other hand, the formation of (*R*)-(+)-phosphine oxide (LIV) on treating (−)-methylphenylphosphinothiolate (LVIII) with n-propylmagnesium bromide proved that, in contrast to *S*-methyl phosphonothiolates, methyl phosphinothiolates react with Grignard reagents, at the same time undergoing an inversion of the configuration at the phosphorus atom.

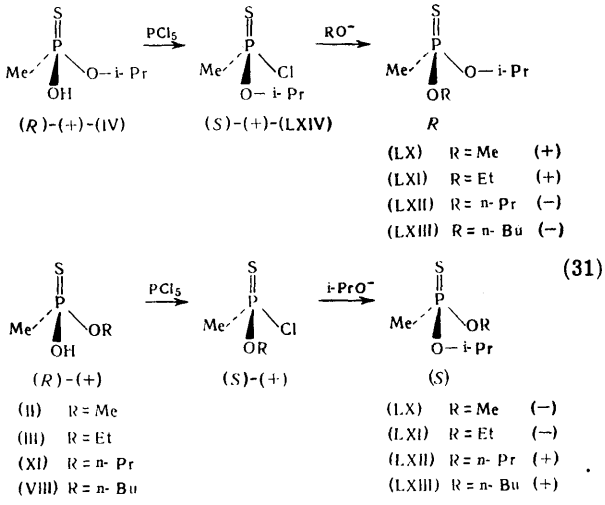
Recently, Mikołajczyk et al.[81] determined the absolute configurations of a series of optically active *O*-alkyl alkylphosphonothioic acids using (*R*)-(+)-*O*-isopropyl methylphosphonothioic acid as the configuration standard. The chemical correlation was based on the stereospecific two-stage conversion of the thioacids into optically active phosphonothionates:



(30)

According to the results of previous studies, both the reaction of the thioacids with phosphorus pentachloride and the substitution of the chlorine atom in phosphonochloridothionates by an alkoxy-group proceed with inversion of the configuration at the phosphorus atom.

The chemical correlation between the configurations of dextrorotatory *O*-alkyl methylphosphonothioic acids is illustrated below:



(31)

(*R*)-(+)-*O*-isopropyl methylphosphonothioic acid (IV) was converted into the (*S*)-(+)-phosphonochloridothionate (LXIV), from which the corresponding optically active *O*-alkyl *O*-isopropyl methylphosphonothioates (LX–LXIII) with the (*R*)-configuration were obtained as a result of reactions with alkoxides RO^- (R = Me, Et, n-Pr, or n-Bu).

On the other hand, the same reactions of (+)-*O*-alkyl methylphosphonothioic acids (II, III, VIII, and XI) (under the influence of PCl_5 and $i\text{-}PrO^-$) yielded the same esters but with rotations of the opposite sign, i.e. with the opposite configurations. Comparison of both types of thionate esters obtained shows that all the *O*-alkyl methylphosphonothioic acids have the (*R*)-(+)-configuration. The chemical correlation between acids of the *O*-alkyl ethylphosphonothioic (I and V) and *O*-alkyl isopropylphosphonothioic (VI and X) series was carried out in the same way.

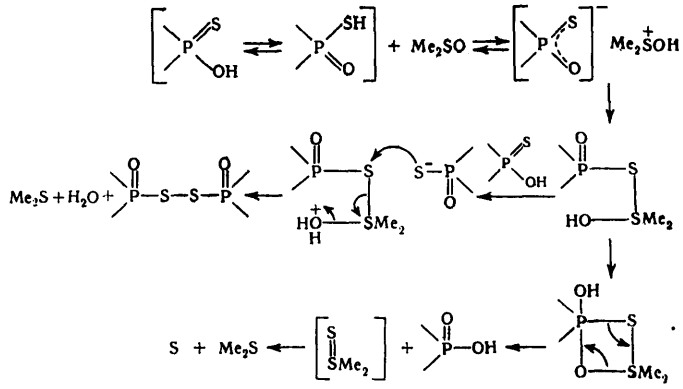
All the results based on chemical correlations show that (+)-*O*-alkyl alkylphosphonothioic acids have the same (*R*)-configuration regardless of the dimensions of the alkyl groups linked directly or by an oxygen bridge to the phosphorus atom.

V. ASYMMETRIC REDUCTION OF SULPHOXIDES BY OPTICALLY ACTIVE PHOSPHORUS-BASED THIOACIDS

Asymmetric syntheses and reactions in which the racemate is resolved kinetically as well as stereospecific transformations are frequently sources of information about the absolute configurations of the optically active reactants. It may therefore be of interest to examine the results obtained by the authors of the review in a study of the asymmetric reduction of chiral sulphoxides with the aid of optically active phosphorus-based thioacids.

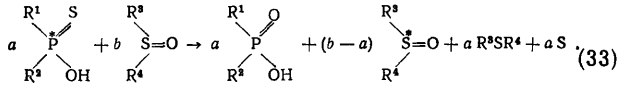
Phosphorus-based thioacids react with sulphoxides in two ways, forming respectively oxygen-containing acids,

sulphides, and elemental sulphur or diphosphoryl disulphides, sulphides, and water[99-102]. The proposed mechanism explained satisfactorily the dual nature of the reaction and the formation of all its products:



(32)

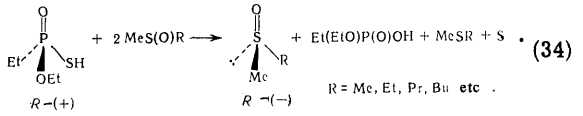
The mode of desulphuration of the acids, usually observed in the presence of an excess of the sulphoxide, constitutes an ideal model reaction for the investigation of the asymmetric reduction of chiral sulphoxides. Mikołajczyk and coworkers[48,102] found that, after the reaction of optically active phosphonothioic acids with an excess of racemic sulphoxides, the sulphoxides which failed to react exhibited optical activity, i.e. had been enriched in the more slowly reacting enantiomers:



(33)

Asymmetric reduction is observed also for equimolar amounts of the reactants and when the reaction has not gone to completion.

It must be emphasised that, regardless of whether the sulphoxide has been used in an excess of in an equimolar amount, the mode of the asymmetric reaction is the same. Thus alkyl methyl sulphoxides with the (S)-configuration always react faster with the dextrorotatory (*R*)-(+)-*O*-ethylphosphonothioate [so that the enantiomer with the (*R*)-configuration predominates after isolation in the sulphoxide which failed to react] and conversely:

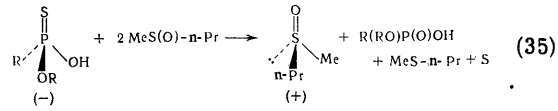


(34)

This has also been confirmed for allyl methyl sulphoxide, whose (−)- and (+)-isomers have, in contrast to simple saturated alkyl methyl sulphoxides, the (*S*)- and (*R*)-configurations respectively.

The above results show that there is a definite relation between the chirality of the optically active thioacid and the chirality of the sulphoxides which react with it. This relation is shown to an even more marked extent in the asymmetric reduction of methyl n-propyl sulphoxide, which has been investigated with the aid of a series of optically active *O*-alkyl alkylphosphonothioic acids. The results of these studies are presented in Table 5.

They show that in all cases the sulphoxide, recovered after the reaction with the (*S*)-(−)-thioacid was dextrorotatory, i.e. contained an excess of the (*S*)-enantiomer, while the sulphoxide regenerated after the reaction with the (*R*)-(+)-thioacid had the *R*-(−)-configuration:



(35)

Table 5. Asymmetric reduction of methyl n-propyl sulphoxide by *O*-alkyl alkylphosphonothioic acids $(RO)R^1P(S)OH$.

No.	R	R^1	Thioacid		Sulphoxide	
			$[\alpha]_D$, °	absolute configuration	$[\alpha]_D$, °	absolute configuration
II	Me	Me	−2.89	*S*	+1.33	*S*
			+2.14	*R*	−1.27	*R*
III	Et	Me	−9.75	*S*	+4.47	*S*
			+10.72	*R*	−3.51	*R*
XI	n-Pr	Me	−1.03	*S*	+0.32	*S*
			+1.30	*R*	−0.35	*R*
IV	i-Pr	Me	−13.9	*S*	+1.29	*S*
			+12.6	*R*	−3.66	*R*
VIII	n-Bu	Me	−12.6	*S*	+3.30	*S*
			+13.02	*R*	−3.34	*R*
V	Me	Et	−8.34	*S*	+2.80	*S*
			+4.70	*R*	−1.78	*R*
I	Et	Et	−13.50	*S*	+5.27	*S*
			+12.90	*R*	−4.92	*R*
X	Me	i-Pr	−13.00	*S*	+0.58	*S*
			−14.67	*R*	−2.17	*R*
VI	Et	i-Pr	+21.54	*S*	+6.45	*S*
			+7.34	*R*	−2.97	*R*

The existence of a definite relation between the chirality of the thioacids and sulphoxides in the reaction being analysed not only demonstrates the possibility of the employment of this reaction to determine the relative or absolute configurations of phosphorus-based thioacids but also consitutes a basis for a model of the transition state in the asymmetric reduction process.

VI. THE APPLICATION OF NMR IN THE DETERMINATION OF THE OPTICAL PURITIES AND CONFIGURATIONS OF OPTICALLY ACTIVE PHOSPHORUS-BASED THIOACIDS

According to general considerations concerning the symmetry of species[103], the groups of nuclei or single nuclei having the same chemical environment either externally or internally, which cannot be interchanged by any symmetry operation, are in a diastereotopic environment in both achiral and chiral solvents. Such nuclei are anisochronic and as a rule should exhibit different chemical shifts and different spin–spin coupling constants. In contrast to these, enantiopic nuclei are screened to the same extent in achiral solvents and are isochronic. However, in chiral solvents or in achiral solvents containing chiral paramagnetic shift reagents, these nuclei become diastereotopic.

These relations make it possible to apply NMR to determine the optical purities of chiral compounds. It permits the determination of the composition of the diastereoisomers obtained from a mixture of enantiomers

and an optically pure reagent (stable diastereoisomers) or to determine the enantiomeric composition in chiral solvents or in achiral solvents containing chiral paramagnetic shift reagents (dynamic diastereoisomeric systems).

The magnetic non-equivalence of diastereoisomers in which the chiral centres are linked covalently in a single molecule was noted for the first time by Mateos and Cram[104]. This phenomenon was used to determine the optical purities of many chiral organic compounds[105,106]. A similar effect was observed by Pirkle and Beare[107] for a mixture of enantiomers in optically active solvents. Here unstable solvation diastereoisomers are formed in consequence of the interaction between the solute and the solvent (for example, as a result of the formation of hydrogen bonds). Because of this, the enantiomers have different chemical environments, which is the reason for the appearance of the magnetic non-equivalence in the NMR spectra.

Pirkle also found that, within the limits of a single class of compounds, the signals corresponding to enantiomers with the same configuration shift in the same direction relative to the signals corresponding to enantiomers with opposite configurations. He called this phenomenon *the sense of magnetic non-equivalence* (*s.m.n.*). Thus, when the signals of the given enantiomer are located in a weaker field, the enantiomer exhibits a "low" *s.m.n.*, while the enantiomer with the opposite configuration is characterised by a "high" *s.m.n.* Knowing the configuration and the *s.m.n.* of a single representative of a given class of compounds, it is possible to determine the configuration of any other compound in this class on the basis of NMR spectra alone.

Diastereoisomeric salts are systems in which there are stronger interactions between the components (acid–base) than in the solvation diastereoisomers investigated by Pirkle. Therefore the NMR spectra of diastereoisomeric salts should presumably also be different and the magnetic non-equivalences $\Delta\delta$ should be more marked.

The magnetic non-equivalence in systems of this type was noted for the first time by Horeau and coworkers[108], who studied the NMR spectra of diastereoisomeric chiral salts of carboxylic acids with optically active α-phenylethylamine.

Mikołajczyk and coworkers[47,109,110], continuing the studies on the absolute configurations of chiral phosphorus-based thioacids, found that they form with optically active amines diastereoisomeric dynamic systems, which give

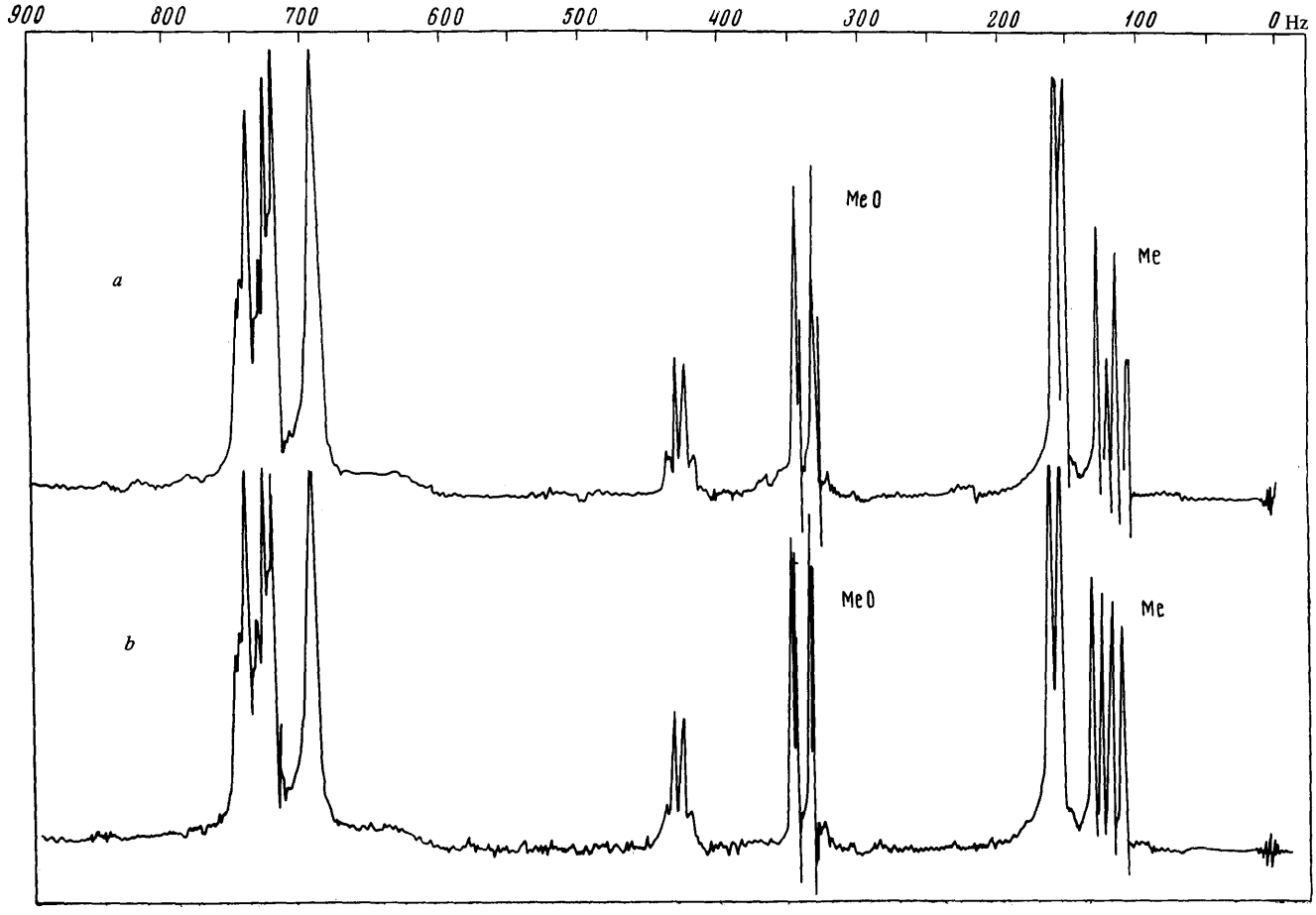
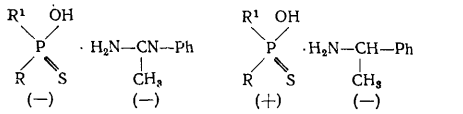


Figure 1. ^{1}H NMR spectra of the diastereoisomeric salts of *O*-methyl methylphosphonothioic acid (II) with (–)-α-phenylethylamine: *a*) 70% of (*S*)-(–)-(II); *b*) racemic (II).

rise to ^{1}H and ^{31}P NMR spectra. Optically active α-phenylethylamine was used in these studies because of the ready availability of both its enantiomers, the ready solubility of its salts in non-polar solvents, and also because they are usually employed for the optical resolution of phosphorus-based thioacids:



The magnetic non-equivalence of *O*-alkyl methylphosphonothioic acids is most effectively observed on the basis of signals due to the *P*-methyl group and that of the class of *O*-methyl alkylphosphonothioic acids on the basis of signals due to the methoxy-group. The ^{1}H NMR spectra of diastereoisomeric salts of *O*-methyl methylphosphonothioic acid presented in Fig. 1 illustrate these two cases.

Fig. 2 presents the ^{31}P NMR spectra of diastereoisomeric salts of *O*-isopropyl methylphosphonothioic acid.

The application of a double resonance technique by Mikołajczyk and Omelańczuk[47,110], as a result of which the ^{31}P NMR spectra of the diastereoisomeric salts are simplified to two single signals corresponding to the enantiomeric acids, merits special attention. Fairly large chemical shifts $\Delta\delta$ are then observed (Table 6), which makes it possible to determine readily the enantiomeric compositions and hence the optical purities of the chiral phosphorus-based thioacids[59,63].

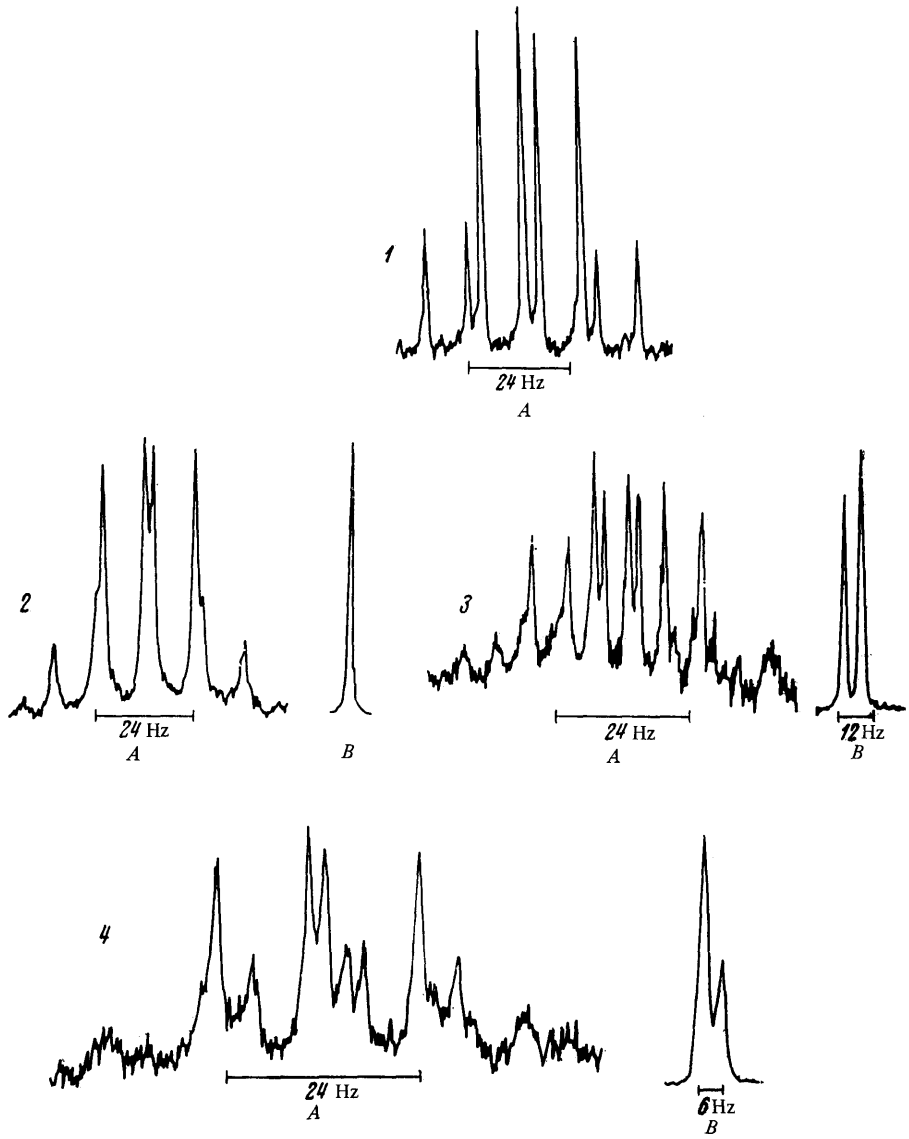


Figure 2. ^{31}P NMR spectra of the diastereoisomeric salts of *O*-isopropyl methylphosphonothioic acid (IV) with α-phenylethylamine (PhEA): *A*) fundamental spectra; *B*) double resonance spectra; 1) (±)-(IV); 2) (±)-(IV).(±)-PhEA; 3) (±)-(IV).(−)-PhEA; 4) (−)-(IV).(−)-PhEA [the thioacid (IV) in which the (−)-enantiomer predominated was used].

Furthermore, it has been noted that a low *s.m.n.* is characteristic of all *O*-alkyl alkylphosphonothioic acids with the (*S*)-configuration and, as for solvation diastereoisomers, remains unchanged within the limits of a single class of compounds. Thus the magnetic non-equivalence of diastereoisomeric salts can also be used to determine the relative or absolute configurations of phosphorus-based thioacids.

Table 6. The magnetic non-equivalences Δδ and *s.m.n.* for the diastereoisomeric salts of phosphorus-based thioacids with (−)-α-phenylethylamine.

Thioacid	Δδ*, Hz ^{1}H NMR**	Δδ, Hz ^{31}P NMR***	*s. m. n.*
Me (MeO) P (S) OH (*II*)	9.2	2.0	low for (*S*)-(−)-
Me (EtO) P (S)OH (III)	18.9	2.1	low for (*S*)-(−)-
Me (i-PrO) P (S) OH (IV)	7.0	6.4	low for (*S*)-(−)-
Me (n-PrO) P (S) OH (XI)	6.9	3.9	low for (*S*)-(−)-
Me (BuO) P (S) OH (VIII)	18.6	3.5	low for (*S*)-(−)-
Et (MeO) P (S) OH (V)	2.9	2.1	low for (*S*)-(−)-
i-Pr (MeO) P (S) OH (X)	0.6	1.2	low for (*S*)-(−)-
t-Bu (MeO) P (S) OH (IX)	4.2	—	—
Et (EtO) P (S) OH (I)	—	2.1	low for (*S*)-(−)-
i-Pr (EtO) P (S) OH (VI)	—	1.1	low for (*S*)-(−)-

* The values of Δδ refer to racemic salts of the thioacids.

** The spectra were obtained on a Varian-HR-60 apparatus in a 60 MHz field in the presence of tetramethylsilane as the internal standard. Groups containing the protons for which the Δδ are quoted have been underlined.

*** The spectra were obtained by a double resonance technique on an INM-60-HL apparatus in a 24.3 MHz field in the presence of phosphoric acid as the internal standard.

The results of studies on the dependence of the magnetic non-equivalence on temperature, the solvent, and concentration[111] suggest that in non-polar solvents there is an acid–base equilibrium:

$$A_RH + A_SH + 2B_R \begin{cases} \xrightarrow{k_1} A_RHB_R \overset{k_3}{\rightleftarrows} A_R^- + B_RH^+ \\ \xrightarrow{k_2} A_SHB_R \overset{k_4}{\rightleftarrows} A_{(S)}^- + B_{(R)}H^+ \end{cases} \quad (36)$$

The undissociated salts, i.e. A_RHB_R and A_SHB_R, the existence of which in the form of ion pairs is favoured by the non-polar medium and the low temperature, are responsible for the observed magnetic non-equivalence. A more detailed mathematical approach to the problem of diastereoisomeric dynamic systems has been described elsewhere[112,113].

The measurement of the magnetic non-equivalence of diastereoisomeric salts has been finding increasing application in the determination of the optical purities and configurations of other chiral compounds[114–118], particularly since the majority of them are in fact resolved by the classical method involving the crystallisation of diastereoisomeric salts.

VII. CIRCULAR DICHROIC STUDIES ON OPTICALLY ACTIVE PHOSPHORUS-BASED THIOACIDS

Following the development of accurate spectrophotometric apparatus, methods for the determination of configurations based on the use of the phenomenon of optical rotatory dispersion (ORD) and circular dichroism (CD) have assumed increasing importance recently[119]. Since CD spectra are more readily susceptible to analysis, particularly for complex organic molecules containing various functional groups, CD is more widely used to determine the configurations of chiral molecules. CD spectra for optically active phosphorus-based thioacids yielded valuable information and confirmed the validity of the configurations[120] assigned by other methods.

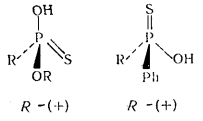
Table 7. The specific rotations $[\alpha]_D$, circular dichroic data, and ultraviolet spectroscopic parameters for *O*-alkyl alkylphosphonothioic acids R(R^{1}O)P(S)OH.

Thioacid R	Thioacid R^1	$[\alpha]_D$ °	Absolute configuration	Solvent	CD: λ_{max}, (nm (Δε)	u.v.: λ_{max}, nm (ε)
Me	Me	+2.8	*R*	isooctane	197 (−1.3)	—
				water	202 (−2.3)	—
Me	Et	+9.5	*R*	isooctane	196 (−2.9)	—
				water	205 (−2.3)	—
Me	n-Pr	+1.3	*R*	isooctane	195 (−0.86)	—
				water	201 (−0.66)	—
Me	i-Pr	+14.7	*R*	isooctane	196 (−3.3)	—
				acetonitrile	197 (−1.5)	—
				ethanol	197 (−1.8)	—
Me	n-Bu	−12.6	*S*	isooctane	198 (+4.4)	—
				water	204 (+2.8)	—
Et	Me	−8.3	*S*	isooctane	199 (+5.2)	190 (9900)
				water	205 (+3.4)	206 (5600)
				ethanol	200 (+1.8)	190 (10 500)
Et	Et	+12.9	*R*	0.5 *N* HCl	200 (+2.7)	—
				isooctane	197 (−2.3)	—
Et	Et	−13.9	*S*	isooctane	197 (+2.3)	—
				ethanol	198 (+1.4)	—
				water	205 (+1.5)	—
i-Pr	Me	−17.0	*S*	water-KOH (pH 12)	213 (+1.3)	—
				isooctane	198 (+2.9)	—
				water	204 (+1.8)	—
i-Pr	Et	−21.3	*S*	isooctane	198 (+4.2)	—
				water	205 (+2.6)	—
t-Bu	Me	+13.2	*R*	isooctane	200 (−5.7)	190 (7150)
				ethanol	202 (−3.5)	185 (8200)
				water	210 (−4.4)	196 (5800)
						207 (4950)
						185 (7700)

The CD spectra for all the *O*-alkyl alkylphosphonothioic acids investigated exhibit only one intense transition near 200 nm, which is shown most distinctly in non-polar solvents. The values of Δε and χ_{max} are listed in Table 7. Evidently the negative Cotton effect is characteristic of acids with the (*R*)-(+)-configuration and the positive effect is characteristic of acids with the (*S*)-(−)-configuration. The position of the absorption band is almost independent of the type of solvent and a distinct bathochromic shift is observed only in water. This is probably a result of the dissociation of the acids P(S)OH and a change in the nature of the chromophoric group.

The CD spectra for alkylphenylphosphinothioic acids (XXI and XX) are much more complex owing to the presence of an aromatic ring in the molecule and contain at least four absorption bands in the region near 270,

230, 215–220, and below 200 nm. The second band can be attributed to the chromophore P(S)OH. It has been observed that both phosphinic acids investigated, with the same signs of optical rotation, are homochiral, i.e. have the same configuration:



R -(+) *R* -(+)

It is noteworthy that the application of conformational asymmetry rules[121] leads to the same conclusion, namely that (+)-*O*-alkyl alkylphosphonothioic and (+)-alkylphenylphosphinothioic acids have the (*R*)-configuration and exist in solution in the thiono-form.

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